

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens*. Proceed as directed in § 436.32(b) of this chapter, using a solution containing 200 milligrams of carbenicillin per milliliter.

(4) [Reserved]

(5) *Moisture*. Proceed as directed in § 436.201 of this chapter.

(6) *pH*. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams of carbenicillin per milliliter (or if packaged for dispensing, use a solution prepared as directed for reconstitution in the labeling).

(7) *Identity*. Proceed as directed in § 436.211 of this chapter, using a 0.5 percent potassium bromide disc prepared as directed in paragraph (b)(1) of that section.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59857, Nov. 22, 1977; 45 FR 22921, Apr. 4, 1980; 50 FR 19918, May 13, 1985; 51 FR 27532, Aug. 1, 1986]

§ 440.15 Cloxacillin sodium monohydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Cloxacillin sodium is the monohydrate sodium salt of 5-methyl-3-(*o*-chlorophenyl)-4-isoxazolyl penicillin. It is so purified and dried that:

(i) Its potency is not less than 825 micrograms of cloxacillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not less than 3 percent and not more than 5 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 4.5 nor more than 7.5.

(v) Its cloxacillin content is not less than 82.5 percent.

(vi) It passes the identity test.

(vii) It is crystalline.

(2) *Labeling*. It shall be labeled in accordance with the requirements of § 432.5 of this subchapter.

(3) *Requests for certification; samples*. In addition to complying with the requirements of § 431.1 of this subchapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH,

cloxacillin content, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency*. Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 5 micrograms of cloxacillin per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in § 436.204 of this subchapter.

(iii) *Hydroxylamine colorimetric assay*. Proceed as directed in § 436.205 of this subchapter.

(2) [Reserved]

(3) *Moisture*. Proceed as directed in § 436.201 of this subchapter.

(4) *pH*. Proceed as directed in § 436.202 of this subchapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Cloxacillin content*. Accurately weigh approximately 100 milligrams of the sample and dissolve in sufficient 5*N* sodium hydroxide to give a total volume of 25 milliliters. Place in a boiling water bath for 30 minutes. Cool, acidify 1 milliliter with 1 milliliter of dilute sulfuric acid (1 in 2), add 8 milliliters of water, and extract with two 25-milliliter portions of ethyl ether. Combine the ether extractives and extract with 25-milliliter portions of 0.1*N* sodium hydroxide. Combine the alkaline extractives and dilute to 100 milliliters with carbon dioxide-free water. Treat a portion of the cloxacillin working standard in the same manner. Using a suitable spectrophotometer, determine the absorbance of the solution in a 1-centimeter cell at the absorption peaks at 257±3 nanometers and at 282±3 nanometers compared with a reagent blank. Determine the percent

cloxacillin in the sample by means of the following calculation:

$$\text{Percent cloxacillin} = \frac{A_1 \times \text{weight of standard in milligrams, on an "as is" basis} \times \text{percent cloxacillin in the standard}}{A_2 \times \text{weight of sample in milligrams on an "as is" basis} \times 100}$$

where:

A₁=Difference in absorbance for the sample between 257 nanometers and 282 nanometers;

A₂=Difference in absorbance for the cloxacillin working standard, similarly treated.

(6) *Identity*. Proceed as directed in § 436.211 of this subchapter, using the 0.5 percent potassium bromide disc described in paragraph (b)(1) of that section.

(7) *Crystallinity*. Proceed as directed in § 436.203 of this subchapter.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59857, Nov. 22, 1977; 50 FR 19918, May 13, 1985]

§ 440.17 Cyclacillin.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Cyclacillin is 6-(1-aminocyclohexanecarboxamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. It is a white to off-white powder. It is so purified and dried that:

(i) It contains not less than 900 micrograms and not more than 1,050 micrograms of cyclacillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not more than 1.0 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 4.0 and not more than 6.5.

(v) Its cyclacillin content is not less than 90 percent on an anhydrous basis.

(vi) The acid-base titration concordance is such that the difference between the percent cyclacillin content when determined by nonaqueous acid titration and nonaqueous base titration is not more than six. The potency-acid titration concordance is such that

the difference between the potency value divided by 10 and the percent cyclacillin content of the sample determined by the nonaqueous acid titration is not more than six. The potency base titration concordance is such that the difference between the potency value divided by 10 and the percent cyclacillin content of the sample determined by the nonaqueous base titration is not more than six.

(vii) It is crystalline.

(viii) It gives a positive identity test for cyclacillin.

(2) *Labeling*. In addition to the labeling requirements of § 432.5 of this chapter, each package shall bear on its outside wrapper or container and the immediate container the following statement, "For use in the manufacture of nonparenteral drugs only."

(3) *Requests for certification; samples*. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, cyclacillin content, concordance, crystallinity, and identity.

(ii) Samples required: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay—(1) Potency*. Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient sterile distilled water to give a stock solution containing 1 milligram of cyclacillin per milliliter (estimated). Further dilute an aliquot of the stock